Point-of-care Coagulation Monitoring: Current Status of Viscoelastic Techniques

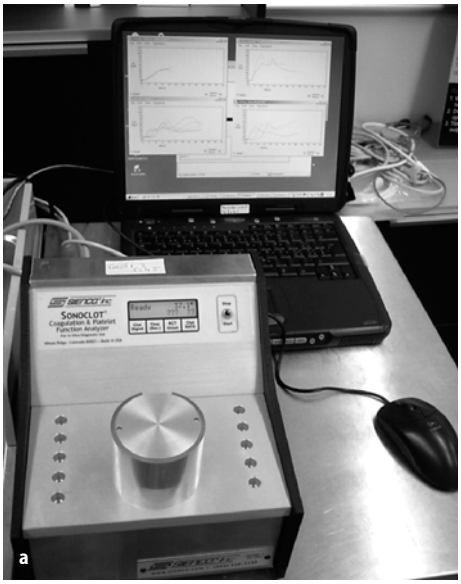
M.T. Ganter and C.K. Hofer

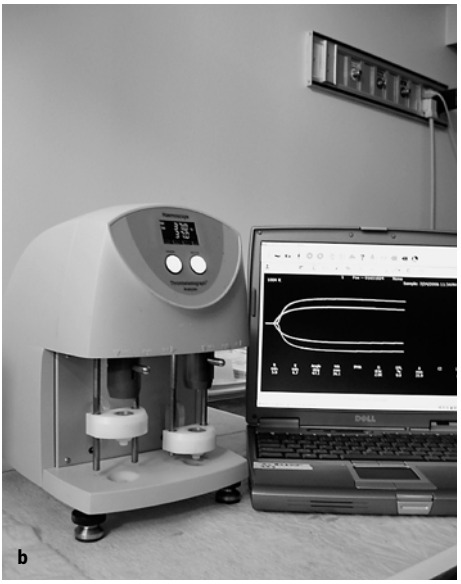
Introduction

Hemostasis monitoring is becoming increasingly important in the management of bleeding patients in the operating room (OR) and the intensive care unit (ICU) in order to improve outcome and reduce costs of treatment. It has been shown in cardiac surgery that frequent reassessment of the coagulation status and transfusion according to well-structured algorithms reduced blood loss and blood component use when compared with transfusion regimens based on clinician discretion [1, 2]. Routine laboratory based coagulation tests (e.g., prothrombin time [PT]/international normalized ratio [INR], activated partial thromboplastin time [aPTT], fibrinogen) measure clotting times and factors in recalcified plasma after activation with different coagulation activators. Platelet numbers are given to complete overall coagulation assessment. Although the values obtained by routine coagulation testing are accurate, standardized, and have been used for a long time, their use has been questioned in the assessment of a severely bleeding patient because values are measured in plasma, no information on platelet function is available, and there is a time delay of 30–60 min from sampling to obtaining the results.

Point-of-care coagulation monitoring may overcome several limitations of routine coagulation testing. Blood is analyzed at the 'bedside' close to the patient and not necessarily in the central laboratory. The coagulation status is assessed in whole blood, better describing physiological clot development by letting the plasma coagulation system interact with platelets and red blood cells (RBCs). Therefore, these techniques may also provide useful information on platelet function. Furthermore, results are available earlier and clot development can be visually displayed real-time using certain devices. According to their main objective and function, point-of-care coagulation analyzers can be classified as follows: Instruments analyzing plasmatic coagulation (e.g., activated clotting time [ACT] or heparin management devices [3]), platelet function (e.g., Platelet Function Analyzer [PFA]-100® [4]), and techniques assessing combined plasmatic coagulation, platelet function, and fibrinolytic system (viscoelastic techniques: Sonoclot® and TEG®/ROTEM®).

This chapter focuses on viscoelastic techniques for perioperative coagulation monitoring of the critically ill patient. The basic principles and properties of the different techniques are summarized, their clinical use is outlined, and the specific ability to monitor different pharmacological substances that interact with hemostasis is presented. Viscoelastic techniques for measuring coagulation have also been used in the hemostasis laboratory for coagulation testing of certain hemostatic disorders or syndromes, but this goes beyond the scope of the current chapter.





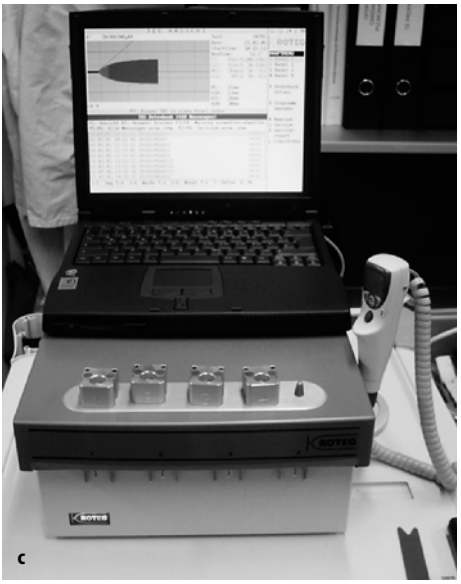


Fig. 1. Viscoelastic point of care coagulation devices **a** Sonoclot®; **b** TEG®; **c** ROTEM®

Sonoclot Analysis

The Sonoclot Analyzer (Fig. 1a, Sonoclot® Coagulation & Platelet Function Analyzer, Sienco Inc., Arvada, CO) was introduced in 1975 by von Kaulla et al. [5]. The principle of the Sonoclot analysis has been described recently in detail [6]. Briefly, Sonoclot measurements are based on the detection of viscoelastic changes of a whole blood or plasma sample. To start a measurement, a hollow, open ended, disposable plastic probe is mounted on the transducer head. Then, 360 µl of test sample is added to the cuvette containing different coagulation activators/inhibitors and calcium (to recalcify citrated blood samples). After an automated mixing procedure, the probe is immersed into the sample and oscillates vertically in the sample. The

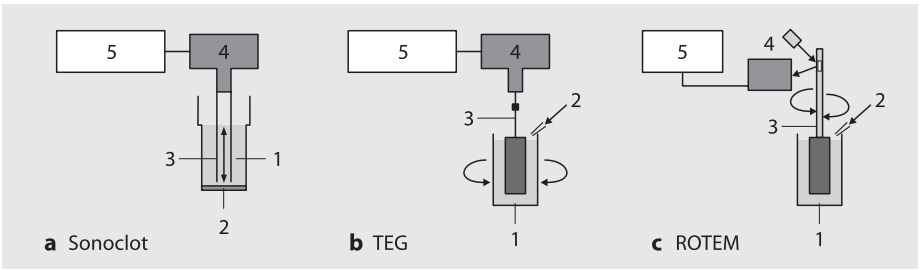


Fig. 2. Working principles of viscoelastic point of care coagulation devices. **a** Sonoclot®: Blood sample in cuvette (1) containing activator (2), disposable plastic probe (3) oscillating in blood sample mounted on electromechanical transducer head (4), data processing (5). **b** TEG®: rotating cup with blood sample (1), coagulation activator (2), pin and torsion wire (3), electromechanical transducer (4), data processing (5). **c** ROTEM®: Cuvette with blood (1), activator added by pipetting (2), pin and rotating axis (3), electromechanical signal detection via light source and mirror mounted on axis (4), data processing (5). For detailed description see text.

changes in impedance to movement imposed by the developing clot are measured (Fig. 2a). Different cuvettes with different coagulation activators/inhibitors are commercially available (Table 1). Normal values for tests run by the Sonoclot Analyzer depend largely on the type of sample (whole blood versus plasma, native versus citrated sample) and type of cuvette used (Table 2).

The Sonoclot Analyzer provides information on the entire hemostasis process, both in a qualitative graph, known as the Sonoclot Signature (Fig. 3) and as quantitative results: The ACT, the clot rate (CR) and the platelet function (PF). The ACT is the time in seconds from the activation of the sample until the beginning of fibrin formation. This onset of clot formation is defined as a certain upward deflection of the Sonoclot Signature and is detected automatically by the machine. Sonoclot's ACT corresponds to the conventional ACT measurement, provided that cuvettes containing a high concentration of typical activators (celite, kaolin) are being used [7–9]. The CR, expressed in Units/min, is the maximum slope of the Sonoclot Signature during initial fibrin polymerization and clot development. Values representing physiologic condition as a function of the activator used are listed in Table 2. PF is reflected by the timing and quality of the clot retraction. PF is a calculated value, derived by using an automated numeric integration of changes in the Sonoclot Signature after fibrin formation has completed (see manufacturer's reference). In order to obtain reliable results for PF, cuvettes containing glass beads for specific platelet activation (gbACT+) should be used [10]. The nominal range of values for the PF goes from 0, representing no PF (no clot retraction and flat Sonoclot Signature after fibrin formation), to approximately 5, representing strong PF (clot retraction occurs sooner and is very strong, with clearly defined, sharp peaks in the Sonoclot Signature after fibrin formation).

The Sonoclot Analyzer has been criticized because its results are influenced by age, sex, and platelet count [11]. Additionally, studies showed poor reproducibility of some of the measured parameters, especially CR and PF [12, 13]. However, others found the Sonoclot Analyzer to be valuable and reliable in patients undergoing cardiac surgical procedures [14, 15] and the Sonoclot Analyzer has even demonstrated a precision close to that of thrombelastography [16]. In more recent studies, test variability of ACT values determined by Sonoclot were comparable to other established

Table 1. Commercially available tests for viscoelastic point-of-care coagulation devices.

Assay	Activator inhibitor	Proposed indication
Sonoclot® Coagulation and Platelet Function Analyzer		
SonACT	Celite	High dose heparin management without aprotinin
kACT	Kaolin	High dose heparin management with/without aprotinin
aiACT	Celite + Clay	High dose heparin management with aprotinin (aprotinin-insensitive ACT)
gbACT+	Glass beads	Overall coagulation and platelet function assessment
H-gbACT+	Glass beads + Heparinase	Overall coagulation and platelet function assessment in presence of heparin; detection of heparin
microPT*	1:1000 TF	Extrinsic pathway; monitoring recombinant activated factor VIIa
Native	None	Non-activated assay Also used to run custom hemostasis tests
Thrombelastograph Hemostasis system (TEG®)		
Kaolin	Kaolin	Overall coagulation assessment and platelet function
Heparinase	Kaolin + Heparinase	Specific detection of heparin (modified Kaolin test adding heparinase to inactivate present heparin)
Platelet Mapping	ADP Arachidonic acid	Platelet function, monitoring antiplatelet therapy (aspirin, ADP-, GPIIb/IIIa inhibitors)
Native	None	Non-activated assay Also used to run custom hemostasis tests
Rotation Thrombelastometry (ROTEM®)		
EXTEM	TF	Extrinsic pathway; fast assessment of clot formation and fibrinolysis
INTEM	Contact activator	Intrinsic pathway; assessment of clot formation and fibrin polymerization
FIBTEM	TF + GPIIb/IIIa antagonist	Qualitative assessment of fibrinogen levels
APTEM	TF + Aprotinin	Fibrinolytic pathway; fast detection of fibrinolysis when used together with EXTEM
HEPTEM	Contact activator + Heparinase	Specific detection of heparin (modified INTEM test adding heparinase to inactivate present heparin)
ECATEM	Ecarin	Management of direct thrombin inhibitors (e.g., hirudin, argatroban)
TIFTEM*	1:1000 TF	Extrinsic pathway; monitoring recombinant activated factor VIIa
NATEM	None	Non-activated assay Also used to run custom hemostasis tests

ACT: activated clotting time; TF: tissue factor; ADP: adenosine diposphate; GPIIb/IIIa: glycoprotein IIb/IIIa receptor. *For research use only (not yet on the market in 2006).

Assay	Activated clotting time (ACT)	Clot Rate (CR)
SonACT	85 – 145 sec	15 – 45 Clot Signal Units/min
kACT	94 – 178 sec	15 – 33 Clot Signal Units/min
gbACT+	119 – 195 sec	7 – 23 Clot Signal Units/min
aiACT	62 – 93 sec	22 – 41 Clot Signal Units/min

Table 2. Reference values for Sonoclot® tests (native whole blood).

For specific details on assays, see Table 1.

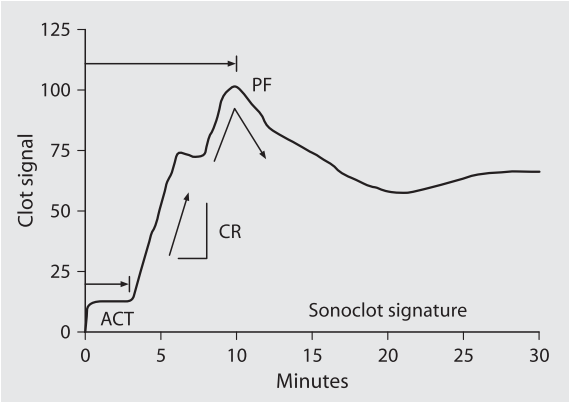


Fig. 3. Typical Sonoclot® Signature ACT: activated clotting time; CR: clot rate; PF: platelet function.

ACT analyzers (8 – 9 % on average) [7 – 9]. Furthermore, test variability for PF determined by gbACT+ and H-gbACT+ (heparinase glass-bead test) was 6 – 10 % in a recent study assessing PF after administration of the glycoprotein IIb/IIIa (GPIIb/IIIa) antagonist, tirofiban, with or without heparin [10].

Thrombelastography, Thrombelastometry

Thrombelastography is a method to assess overall coagulation function and was first described by Hartert in 1948 [17]. Because the thrombelastograph measures the shear elasticity of the blood sample, thrombelastography is sensitive to all interacting cellular and plasmatic components such as coagulation and fibrinolysis. The thrombelastograph measures and graphically displays the time until initial fibrin formation, the kinetics of fibrin formation and clot development, and the ultimate strength and stability of the fibrin clot as well as fibrinolysis. In the earlier literature, the terms thrombelastography, thrombelastograph and TEG were used generically. However, in 1996, thrombelastograph® and TEG® became a registered trademark of the Hemoscope Corporation (Niles, IL, USA) and from that time on these terms have been employed to describe the assay performed using Hemoscope instrumentation only. Alternatively, Pentapharm GmbH (Munich, Germany) markets a modified instrumentation using the terminology rotation thrombelastometry, ROTEM®.

The TEG® (Fig. 1b) measures the clot's physical property by the use of a stationary cylindrical cup that holds the blood sample and is oscillated through an angle of 4°45'. Each rotation cycle lasts 10 seconds. A pin is suspended in the blood by a torsion wire and is monitored for motion (Fig. 2b). The torque of the rotation cup is transmitted to the immersed pin only after fibrin-platelet bonding has linked the cup and pin together. The strength of these fibrin-platelet bonds affects the magni-

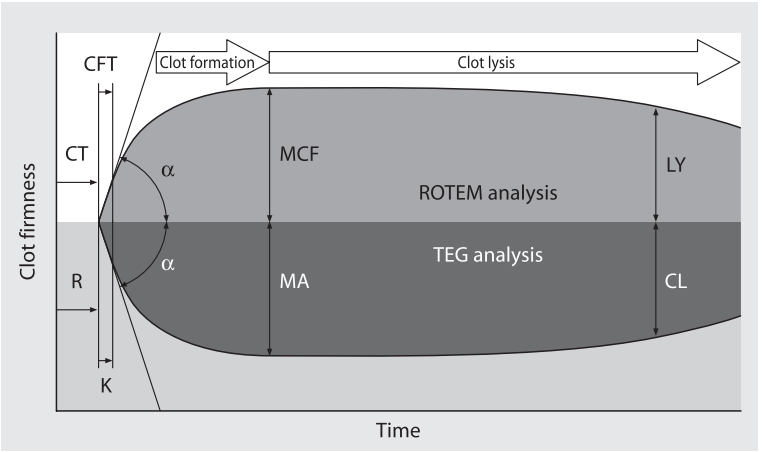


Fig. 4. Typical TEG/ROTEM® tracing. R: reaction time; K: kinetics; α: slope between R and K; MA: maximum amplitude; CL: clot lysis; CT: clotting time; CFT: clot formation time; α: slope of tangent at 2 mm amplitude; MCF: maximal clot firmness; LY: Lysis. For detailed description and reference values please see Tables 2 and 3.

tude of the pin motion. Thus, the output is directly related to the strength of the formed clot. As the clot retracts or lyses, these bonds are broken and the transfer of cup motion is again diminished. The rotation movement of the pin is converted by a mechanical-electrical transducer to an electrical signal finally being displayed as the typical TEG® tracing (Fig. 4). The ROTEM® technology (Fig. 1c) avoids some limitations of traditional instruments for thrombelastography, especially the susceptibility to mechanical shocks. Signal transmission of the pin suspended in the blood sample is carried out via an optical detector system, not a torsion wire and the movement is initiated from the pin, not the cup (Fig. 2c).

Most common tests for both technologies are listed in Table 1. The TEG® and ROTEM® technology are comparable and show similar tracings (Fig. 4) but nomenclature and reference ranges are different (Table 3). The repeatability of measurements by both devices has been shown to be acceptable, provided they are performed exactly as outlined in the user manuals. For example, coefficients of variation using kaolin activated TEG® were 13% for reaction time (R), 4% for kinetics (K), 3% for α, and 6% for maximum amplitude (MA) (TEG® 5000 User Manual) and 3–12% for coagulation time (CT) and clot formation time (CFT, intrinsic-, extrinsic-TEM), 1–5% for α and maximum clot firmness (MCF, intrinsic-, extrinsic-TEM), and 6–13% for MCF (fibrinogen [FIB]-TEM) [18].

Comparing Viscoelastic Techniques with Standard Hemostatic Laboratory Tests

Conventional laboratory coagulation tests are usually performed in plasma and most typically end when fibrin strands are formed. However, viscoelastic tests are whole blood assays measuring the entire clotting process from fibrin formation to clot retraction and lysis. Several studies have compared results from viscoelastic techniques to laboratory coagulation data. It is not surprising that point-of-care

Table 3. Nomenclature and reference values of thrombelastography (TEG®) and thrombelastometry (ROTEM®).

	TEG®	ROTEM®
Clotting time (period to 2 mm amplitude)	R (reaction time) N (WB) 4–8 min N (Cit) 3–8 min	CT (clotting time) N (Cit, INTEM) 137–246 sec N (Cit, EXTEM) 42–74 sec
Clot kinetics (period from 2 to 20 mm amplitude)	K (kinetics) N (WB) 1–4 min N (Cit) 1–3 min	CFT (clot formation time) N (Cit, INTEM) 40–100 sec N (Cit, EXTEM) 46–148 sec
Clot strengthening (alpha angle)	α (slope between r and k) N (WB) 47–74° N (Cit) 55–78°	α (slope of tangent at 2mm amplitude) N (Cit, INTEM) 71–82° N (Cit, EXTEM) 63–81°
Amplitude (at set time)	A	A
Maximum strength	MA (maximum amplitude) N (WB) 55–73 mm N (Cit) 51–69 mm	MCF (maximum clot firmness) N (Cit, INTEM) 52–72 mm N (Cit, EXTEM) 49–71 mm N (Cit, FIBTEM) 9–25 mm
Lysis (at fixed time)	CL30, CL60	LY30, LY60

TEG®: N = normal values for kaolin activated TEG® in native whole blood (WB) or citrated and recalcified blood samples (Cit) (Hemoscope Corp.). ROTEM®: N = normal values for contact (INTEM), tissue factor (EXTEM) and tissue factor plus GPIIb/IIIa inhibitor (FIBTEM) activated citrated and recalcified blood samples [18]. Reference values depend on reference population, blood sampling technique, other pre-analytical factors and coagulation activator.

clotting times (ACT, R, CT) showed a trend in the same direction as laboratory based clotting times, depending on the activator used. Therefore, a whole blood sample from a heparinized patient or a patient with hemophilia (factor VIII or IX deficiency) will show a significantly prolonged CT if a contact activator is used. However, there is a more obvious association between the maximum strength MA/MCF of the TEG/ROTEM® signature and both platelet count (or function) and fibrinogen concentration [19, 20]. To finally determine the fibrinogen influence, tests can be performed eliminating platelet function by a GPIIb/IIIa inhibitor (e.g., fibTEM). This concept has been proven to work and a good correlation of this modified MA/MCF with fibrinogen levels determined by the Clauss method has been shown ($r = 0.85$ [TEG® 5000 User Manual] and $r = 0.75$ [21]).

Cardiac Surgery and Postoperative Care

Coagulation management of patients undergoing cardiac surgery is complex because of a delicate balance between anticoagulation for cardiopulmonary bypass (CPB) and hemostasis after CPB. During CPB, optimal anticoagulation dictates that coagulation is antagonized and platelets are prevented from activation so that microvascular clots do not form on the extracorporeal circuit. After surgery, coagulation abnormalities, platelet dysfunction, and fibrinolysis can occur, creating a situation whereby hemostatic integrity must be restored. The complex process of anticoagulation with heparin, antagonism with protamine, and postoperative hemostasis therapy cannot be performed without careful and accurate monitoring.

ACT is currently used in clinical practice to monitor heparin therapy during CPB correlating well with heparin concentration, mainly before going on CPB [7–9, 22]. The Sonoclot Analyzer, measuring the ACT, has been used to guide heparin management for CPB in the presence or absence of aprotinin and the accuracy and performance has been shown to be comparable to standard ACT machines [7–9]. Furthermore, the Sonoclot Analyzer has been shown to reliably detect pharmacological GPIIb/IIIa inhibition [10, 23] and successfully used to assess the coagulation status and platelet function in patients undergoing cardiac surgery [14].

Viscoelastic point-of-care coagulation devices have been applied, with limited success, to predict excessive bleeding after CPB [24, 25]. However, large prospective [1] and retrospective studies [26] have demonstrated a significant decrease in perioperative and overall transfusion requirement if hemostasis management was guided by TEG®/ROTEM® based algorithms. Interestingly, a recent study by Avidan et al. showed little advantage of a combined transfusion algorithm using TEG® (global coagulation), PFA-100® (platelet function), and Hepcon® (heparinization), over a well-structured laboratory-guided algorithm. Both approaches were able to reduce postoperative blood component usage compared with clinical discretion alone [2].

To detect non-heparin related hemostatic problems even in the presence of large amounts of heparin during CPB, tests with heparinase have been developed for each instrument (Table 1) and an algorithm based upon heparinase-modified TEG® resulted in a significant reduction in hemostatic products [27].

Hepatic Surgery and Postoperative Care

Patients undergoing hepatic surgery and, particularly, orthotopic liver transplantation may have large derangements in their coagulation making point-of-care coagulation monitoring highly desirable. Problems associated with the defective organ (decreased synthesis and clearance of clotting factors, platelet defects) lead to impaired hemostasis and hyperfibrinolysis. Furthermore, systemic complications like sepsis and disseminated intravascular coagulation (DIC) further complicate a pre-existing coagulopathy. Finally, marked changes in hemostasis in orthotopic liver transplantation occur during the anhepatic phase and immediately following organ reperfusion, mainly a hyperfibrinolysis resulting from accumulation of tissue plasminogen activator due to inadequate hepatic clearance and a release of exogenous heparin and endogenous heparin-like substances.

One of the first clinical applications of TEG® was in the hemostatic management of orthotopic liver transplantation and TEG® guided component replacement [19]. Although the value of TEG/ROTEM® in management of patients undergoing orthotopic liver transplantation has been established in the literature [28, 29], only a third of all orthotopic liver transplantation programs in the United States used TEG® routinely according to a national survey in 2002 [30]. In addition to the hemorrhagic risk associated with hepatic surgery and orthotopic liver transplantation, hypercoagulability and thrombotic complications have been described in the postoperative period and can be adequately assessed with TEG/ROTEM® [31, 32]. Only a few studies are available on the use of the Sonoclot Analyzer in hepatic surgery and orthotopic liver transplantation; however, this technique has been found to be useful in the perioperative coagulation management of these patients [33].

Other Applications of Viscoelastic Point-of-care Coagulation Monitoring

Viscoelastic techniques have been used to assess blood coagulation in multiple clinical situations outside the cardiac and hepatic units, but experience is limited. For example, TEG® has been applied to measure the coagulation status in trauma patients [34]. Furthermore, TEG/ROTEM® and Sonoclot® have been used to assess a hypercoagulable state in several clinical settings, e.g., after major abdominal surgery [35], in obstetrics [36], and in uremic patients undergoing a surgical procedure [37]. Finally, there is a long list of publications on the successful use of TEG/ROTEM® and Sonoclot® in other clinical areas, summarized in recent reviews [6, 38, 39].

Monitoring Anticoagulants

ACT measurements to guide heparin therapy and the use of modified point-of-care coagulation tests with heparinase to assess the coagulation status in the absence of the anti-coagulatory effects of heparin have been described above. However, besides the monitoring of unfractioned heparin, studies have shown that treatment with low molecular weight heparin (LMWH) and heparinoids (e.g., danaparoid) can also be assessed with point-of-care viscoelastic tests [40]. Both standard and heparinase-modified tests have to be performed in order to increase the sensitivity of TEG/ROTEM® for the effects of LMWH and heparinoids.

Direct thrombin inhibitors are increasingly being used for different indications. Point-of-care viscoelastic techniques, especially the ecarin clotting time (ecarin directly activates thrombin) are helpful in the assessment of the effects of direct thrombin inhibitors [41].

Platelets play a key role in overall coagulation and assessment of their function is highly desirable (more than the platelet number). Anti-platelet agents typically act to inhibit cyclo-oxygenase 1 (e.g., aspirin [acetylsalicylic acid]), ADP receptors (e.g., clopidogrel), or GPIIb/IIIa receptors (e.g., abciximab, tirofiban). As mentioned above, the Sonoclot Analyzer has been shown to reliably detect pharmacological GPIIb/IIIa inhibition [10, 23]. Furthermore, the MA/MCF from TEG/ROTEM® gives some information on overall platelet function (and fibrinogen levels), but is not sensitive to targeted pharmacological inhibition. Therefore, a more sophisticated and laborious test has been developed recently for the TEG® (PlateletMapping) using arachidonic acid and ADP to selectively activate platelets and determine platelet function in the presence of anti-platelet therapy [42].

Monitoring Pro-Coagulant Therapy

Maintaining an adequate coagulation status is one of the goals in patients with severe hemorrhage besides preserving sufficient blood volume and oxygen carrying capacity. Strategies to support coagulation are based on the underlying cause of bleeding and range from prevention of hypothermia and acidosis, re-warming, transfusion of blood products, selective administration of coagulation factors, and the use of pharmacological agents. Interactions of administered crystalloids and colloids with coagulation have to be considered. For example, progressive hemodilution

with current hydroxyethyl starch solutions still compromises blood coagulation more than gelatin or albumin solutions [43].

Modern practice of coagulation management is based on the concept of specific component therapy and requires rapid diagnosis and monitoring of the pro-coagulant therapy (i.e., clotting times, clot kinetics, and clot strengthening). Fibrinogen is a key coagulation factor (substrate to form a clot) and isolated fibrinogen substitution in severe models of dilutional coagulopathy has been shown to improve clot strength and reduce blood loss [44]. Supplementary administration of prothrombin complex (concentrates of factor II, VII, IX, X, antithrombin III, protein C) additionally improved initiation of coagulation and reversed the dilutional coagulopathy [45]. Fibrinogen levels can be assessed by measuring clot strength (MCF/MA) in presence of platelet inhibition by a GPIIb/IIIa inhibitor (e.g., FIBTEM) [21] or by assessing Sonoclot's CR [46]. Fibrinogen substitution should be considered in a bleeding patient if MCF levels are lower than 9 mm in a FIBTEM test.

Recombinant activated factor VII (rFVIIa) treatment is currently approved for patients with congenital or acquired hemophilia, factor VII deficiency, and Glanzmann's thrombasthenia. However, factor VIIa is increasingly used in off-label indications to control severe bleeding (e.g., major trauma, surgical interventions, intracerebral hemorrhage). The concept is to locally activate the coagulation at sites of tissue factor exposure. The resulting thrombin burst then leads to the formation of a fibrin clot, provided there are sufficient fibrinogen levels. Consensus guidelines have been published for these off-label indications, but it is still unclear how to reliably monitor patients receiving recombinant factor VIIa (rVIIa) [47]. In order to study thrombin generation, modified TEG/ROTEM® parameters (based on the original tracing) have been introduced recently: Maximum velocity of clot formation (maximum rate of thrombus generation, MaxVel), time to reach MaxVel (time to maximum thrombus generation, tMaxVel), and total thrombus generation (area under the curve, TTG) [48]. These parameters are supposed to be more sensitive to rVIIa than standard TEG/ROTEM® parameters and dilute tissue factor should be used as coagulation activator for best sensitivity [39]. In a preliminary study, we were able to monitor the effects of rVIIa *in vitro* after severe hemodilution using the new diluted tissue factor activated tests from Sonoclot (microPT) and the ROTEM® (TIFTEM) [46, 49].

Factor XIII is needed for cross-linking fibrin, therefore, stabilizing the clot, increasing clot strength and resistance to fibrinolysis. There are case reports on patients with unexplained intraoperative bleeding due to decreased factor XIII and subsequent stabilization after substitution. Impaired clot strength and increased lysis have been observed [50].

Antifibrinolytic drugs (aprotinin, tranexamic and epsilon aminocaproic acid) are used mostly in complex cardiac surgery to reduce bleeding and transfusion requirements. Aprotinin may interact with point-of-care coagulation assays, prolonging for example celite-activated ACT tests. Therefore, kaolin or aprotinin-insensitive ACT should be used to guide heparin therapy in these patients [8, 9]. Antifibrinolytic therapy may be predicted *in vitro* in TEG/ROTEM® with certain tests already containing an antifibrinolytic agent (e.g., APTEM). APTEM predictive of a good patient response would then show a significantly improved initiation/propagation phase compared to EXTEM and or disappearance of signs of hyperfibrinolysis. There are no conclusive studies on monitoring desmopressin (DDAVP) therapy so far.

Problems with Point-of-Care Coagulation Monitoring

Several concerns have been raised using viscoelastic point-of-care coagulation tests because these tests are hard to standardize. The blood collection site, processing of the sample (native versus citrated samples, time delay between collection and measurement – for citrated samples a minimum rest time of 30 min is required), patient age and gender may significantly affect the results of these tests [38]. Furthermore, equipment, activators, and other modifications will alter the assay specificity. All these factors have to be considered when interpreting results in the literature and have to be known and standardized when running tests in a single center.

As with all point-of-care devices, there is a concern that the devices are not adequately maintained and that quality controls are not done on a regular basis. Using such an instrument for decision making in patient care may harm the patient because of the possibility of incorrectly measured data. Furthermore, non-laboratory personnel are running these point-of-care tests, which may lead to further errors, if not adequately trained. In an effort to minimize these problems and release the OR/ICU personnel from the burden of maintaining their devices, point-of-care devices have to be at least supervised by the central laboratory. Alternatively, point-of-care coagulation analyzers have been moved into the central laboratory – a trained person runs the viscoelastic coagulation test and the results (evolving signatures) are submitted real-time to the patient's bedside.

Conclusion

Viscoelastic point-of-care coagulation analyzers are being used in certain clinical situations, especially in the management of patients undergoing cardiac and liver surgery. Furthermore, they provide useful information in a large variety of clinical scenarios, e.g., massive hemorrhage, assessment of hypo- and hypercoagulable states, and monitoring of pharmacological treatment with anti- and pro-coagulant agents. The advantage of these techniques is that they have the potential to measure the entire clotting process starting with fibrin formation and continuing through to clot retraction and lysis at the bedside with minimal time delays. Furthermore, physiological clot development is better depicted as a result of whole blood analysis of the coagulation status. However, several problems regarding quality standards have to be considered when using viscoelastic techniques.

References

1. Shore-Lesserson L, Manspeizer HE, DePerio M, Francis S, Vela-Cantos F, Ergin MA (1999) Thromboelastography-guided transfusion algorithm reduces transfusions in complex cardiac surgery. Anesth Analg 88:312 – 319
2. Avidan MS, Alcock EL, Da FJ, et al (2004) Comparison of structured use of routine laboratory tests or near-patient assessment with clinical judgement in the management of bleeding after cardiac surgery. Br J Anaesth 92:178 – 186
3. Shore-Lesserson L (2003) Monitoring anticoagulation and hemostasis in cardiac surgery. Anesthesiol Clin North America 21:511 – 526
4. Harrison P (2005) Platelet function analysis. Blood Rev 19:111 – 123
5. von Kaulla KN, Ostendorf P, von Kaulla E (1975) The impedance machine: a new bedside coagulation recording device. J Med 6:73 – 88
6. Hett DA, Walker D, Pilkington SN, Smith DC (1995) Sonoclot analysis. Br J Anaesth 75: 771 – 776

7. Dalbert S, Ganter MT, Furrer L, Klaghofer R, Zollinger A, Hofer CK (2006) Effects of heparin, haemodilution and aprotinin on kaolin-based activated clotting time: in vitro comparison of two different point of care devices. Acta Anaesthesiol Scand 50:461 – 468
8. Ganter MT, Dalbert S, Graves K, Klaghofer R, Zollinger A, Hofer CK (2005) Monitoring activated clotting time for combined heparin and aprotinin application: an *in vitro* evaluation of a new aprotinin-insensitive test using SONOCLOT. Anesth Analg 101:308 – 314
9. Ganter MT, Monn A, Tavakoli R, et al (2006) Monitoring activated clotting time for combined heparin and aprotinin application: in vivo evaluation of a new aprotinin-insensitive test using Sonoclot. Eur J Cardiothorac Surg 30:278 – 284
10. Tucci MA, Ganter MT, Hamiel CR, Klaghofer R, Zollinger A, Hofer CK (2006) Platelet function monitoring with the Sonoclot analyzer after in vitro tirofiban and heparin administration. J Thorac Cardiovasc Surg 131:1314 – 1322
11. Horlocker TT, Schroeder DR (1997) Effect of age, gender, and platelet count on Sonoclot coagulation analysis in patients undergoing orthopedic operations. Mayo Clin Proc 72:214 – 219
12. McKenzie ME, Gurbel PA, Levine DJ, Serebruany VL (1999) Clinical utility of available methods for determining platelet function. Cardiology 92:240 – 247
13. Ekback G, Carlsson O, Schott U (1999) Sonoclot coagulation analysis: a study of test variability. J Cardiothorac Vasc Anesth 13:393 – 397
14. Miyashita T, Kuro M (1998) Evaluation of platelet function by Sonoclot analysis compared with other hemostatic variables in cardiac surgery. Anesth Analg 87:1228 – 1233
15. Saleem A, Blifeld C, Saleh SA, et al (1983) Viscoelastic measurement of clot formation: a new test of platelet function. Ann Clin Lab Sci 13:115 – 124
16. Forestier F, Belisle S, Contant C, Harel F, Janvier G, Hardy JF (2001) [Reproducibility and interchangeability of the Thromboelastograph, Sonoclot and Hemochron activated coagulation time in cardiac surgery]. Can J Anaesth 48:902 – 910
17. Hartert H (1948) Blutgerinnungstudien mit der Thrombelastographie, einem neuen Untersuchungsverfahren. Klin Wochenschrift 26:557 – 583
18. Lang T, Bauters A, Braun SL, et al (2005) Multi-centre investigation on reference ranges for ROTEM thromboelastometry. Blood Coagul Fibrinolysis 16:301 – 310
19. Kang YG, Martin DJ, Marquez J, et al (1985) Intraoperative changes in blood coagulation and thrombelastographic monitoring in liver transplantation. Anesth Analg 64:888 – 896
20. Zuckerman L, Cohen E, Vagher JP, Woodward E, Caprini JA (1981) Comparison of thrombelastography with common coagulation tests. Thromb Haemost 46:752 – 756
21. Coakley M, Reddy K, Mackie I, Mallett S (2006) Transfusion triggers in orthotopic liver transplantation: a comparison of the thromboelastometry analyzer, the thromboelastogram, and conventional coagulation tests. J Cardiothorac Vasc Anesth 20:548 – 553
22. Bull MH, Huse WM, Bull BS (1975) Evaluation of tests used to monitor heparin therapy during extracorporeal circulation. Anesthesiology 43:346 – 353
23. Waters JH, Anthony DG, Gottlieb A, Sprung J (2001) Bleeding in a patient receiving platelet aggregation inhibitors. Anesth Analg 93:878 – 82
24. Tuman KJ, Spiess BD, McCarthy RJ, Ivankovich AD (1989) Comparison of viscoelastic measures of coagulation after cardiopulmonary bypass. Anesth Analg 69:69 – 75
25. Nuttall GA, Oliver WC, Ereth MH, Santrach PJ (1997) Coagulation tests predict bleeding after cardiopulmonary bypass. J Cardiothorac Vasc Anesth 11:815 – 823
26. Anderson L, Quasim I, Soutar R, Steven M, Macfie A, Korte W (2006) An audit of red cell and blood product use after the institution of thromboelastometry in a cardiac intensive care unit. Transfus Med 16:31 – 39
27. Royston D, von Kier S (2001) Reduced haemostatic factor transfusion using heparinase-modified thrombelastography during cardiopulmonary bypass. Br J Anaesth 86:575 – 578
28. Gillies BS (1995) Thromboelastography and liver transplantation. Semin Thromb Hemost 21 Suppl 4:45 – 49
29. Kang Y (1993) Coagulation and liver transplantation. Transplant Proc 25:2001 – 2005
30. Schumann R (2003) Intraoperative resource utilization in anesthesia for liver transplantation in the United States: a survey. Anesth Analg 97:21 – 8
31. Stahl RL, Duncan A, Hooks MA, Henderson JM, Millikan WJ, Warren WD (1990) A hypercoagulable state follows orthotopic liver transplantation. Hepatology 12:553 – 558

32. Cerutti E, Stratta C, Romagnoli R, et al (2004) Thromboelastogram monitoring in the perioperative period of hepatectomy for adult living liver donation. Liver Transpl 10:289 – 294
33. Chapin JW, Becker GL, Hulbert BJ, et al (1989) Comparison of Thromboelastograph and Sonoclot coagulation analyzer for assessing coagulation status during orthotopic liver transplantation. Transplant Proc 21:3539
34. Schreiber MA, Differding J, Thorborg P, Mayberry JC, Mullins RJ (2005) Hypercoagulability is most prevalent early after injury and in female patients. J Trauma 58:475 – 480
35. Mahla E, Lang T, Vicenzi MN, et al (2001) Thromboelastography for monitoring prolonged hypercoagulability after major abdominal surgery. Anesth Analg 92:572 – 577
36. Sharma SK, Philip J, Wiley J (1997) Thromboelastographic changes in healthy parturients and postpartum women. Anesth Analg 85:94 – 98
37. Pivalizza EG, Abramson DC, Harvey A (1997) Perioperative hypercoagulability in uremic patients: a viscoelastic study. J Clin Anesth 9:442 – 445
38. Luddington RJ (2005) Thrombelastography/thromboelastometry. Clin Lab Haematol 27:81 – 90
39. Sorensen B, Ingerslev J (2005) Tailoring haemostatic treatment to patient requirements – an update on monitoring haemostatic response using thrombelastography. Haemophilia 11 Suppl 1:1 – 6
40. Coppell JA, Thalheimer U, Zambruni A, et al (2006) The effects of unfractionated heparin, low molecular weight heparin and danaparoid on the thromboelastogram (TEG): an in-vitro comparison of standard and heparinase-modified TEGs with conventional coagulation assays. Blood Coagul Fibrinolysis 17:97 – 104
41. Carroll RC, Chavez JJ, Simmons JW, et al (2006) Measurement of patients' bivalirudin plasma levels by a thrombelastograph ecarin clotting time assay: a comparison to a standard activated clotting time. Anesth Analg 102:1316 – 1319
42. Craft RM, Chavez JJ, Bresee SJ, Wortham DC, Cohen E, Carroll RC (2004) A novel modification of the Thrombelastograph assay, isolating platelet function, correlates with optical platelet aggregation. J Lab Clin Med 143:301 – 309
43. Niemi TT, Kuitunen AH (2005) Artificial colloids impair haemostasis. An in vitro study using thromboelastometry coagulation analysis. Acta Anaesthesiol Scand 49:373 – 378
44. Fries D, Krismer A, Klingler A, et al (2005) Effect of fibrinogen on reversal of dilutional coagulopathy: a porcine model. Br J Anaesth 95:172 – 177
45. Fries D, Haas T, Klingler A, et al (2006) Efficacy of fibrinogen and prothrombin complex concentrate used to reverse dilutional coagulopathy--a porcine model. Br J Anaesth 97:460 – 467
46. Ganter MT, Schmuck S, Hamiel CR, Zollinger A, Hofer CK (2006) Monitoring the effects of factor VIIa treatment in-vitro after severe hemodilution (part I – Sonoclot). Anesthesiology 105 (Suppl):A1005 (abst)
47. Vincent JL, Rossaint R, Riou B, Ozier Y, Zideman D, Spahn DR (2006) Recommendations on the use of recombinant activated factor VII as an adjunctive treatment for massive bleeding – a European perspective. Crit Care 10:R120
48. Rivard GE, Brummel-Ziedins KE, Mann KG, Fan L, Hofer A, Cohen E (2005) Evaluation of the profile of thrombin generation during the process of whole blood clotting as assessed by thrombelastography. J Thromb Haemost 3:2039 – 2043
49. Schmuck S, Ganter MT, Hamiel CR, Zollinger A, Hofer CK (2006) Monitoring the effects of factor VIIa treatment in-vitro after severe hemodilution (part II – ROTEM). Anesthesiology 105 (Suppl):A1001 (abst)
50. Wettstein P, Haeberli A, Stutz M, et al (2004) Decreased factor XIII availability for thrombin and early loss of clot firmness in patients with unexplained intraoperative bleeding. Anesth Analg 99:1564 – 1569